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WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 47/06, 31/07, 31/56

A1

(11) International Publication Number: WO 92/07586

(43) International Publication Date: 14 May 1992 (14.05.92)

(21) International Application Number: PCT/GB91/01874

(22) International Filing Date: 25 October 1991 (25.10.91)

(30) Priority data:
9023647.2 31 October 1990 (31.10.90) GB
9023648.0 31 October 1990 (31.10.90) GB

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(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TOPICAL COMPOSITION WITH RETINOID PENETRATION ENHANCER

(57) Abstract

The use of retinoids to act as skin penetration enhancers is disclosed. Topical compositions of retinoids with 16,16 disubstituted androstene steroids are also disclosed. Such compositions have utility in arresting hair loss and promoting hair growth.

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Topical composition with retinoid penetration enhancer

The invention relates to a method of increasing the bioavailability of topically active substances by enhancing penetration of the stratum corneum, and compositions for use therein.

Studies into the properties of vitamin A (retinol) and its use as an oral therapy for a variety of dermatologic disorders for many years have led to the use of retinol and other retinoid compounds, including retinoic acid, in topically applied skin-care products having both cosmetic and therapeutic application.

For example, both retinol and retinoic acid have been used in the treatment of acne. In addition, retinoic acid is described as having utility in reversing the ageing process that occurs in the skin, mediated both intrinsically as a factor of increasing age and extrinsically, for example by prolonged exposure to sunlight.

The utility of retinoid compounds per se in hair-care preparations is also described. For example, WO 82/02833 (BAZZANO) describes the use of retinoid compounds as stimulants of hair-growth and in prolonging the anagen phase of the hair-growth cycle.

European Patent Application No. 89301668.3 (BEECHAM) discloses an effect of retinol esters, a specific class of retinoid compounds, in increasing the diameter of growing hair and their use in hair-care compositions.

Moreover, the use of retinoid compounds in combination with other topically active materials has been disclosed. For example, WO 83/02558 (BAZZANO) describes the use of retinoid compounds in combination with the compound minoxidil which compound is marketed as a topically administrable stimulant

of hair-growth.

According to 'Bazzano', the combination of a retinoid compound and minoxidil produces a 'synergistic' effect; i.e. the combination produces an effect which cannot be produced by either compound separately.

According to 'Bazzano', the 'synergism' is attributed to the different but complementary modes of action of the retinoid component and minoxidil on hair-growth. Minoxidil is described as initiating and promoting vellus hair growth on the scalp and the retinoid is described as acting to sustain the growth of terminal hairs from vellus hairs on the scalp.

Thus the retinoid compound in compositions according to 'Bazzano' is acting as a topically active agent per se rather than enhancing the specific hair-growth properties of minoxidil.

United States Patent No. 4,727,088 (NEUTROGENA) describes a topically applied pharmaceutical preparation for the treatment of acne. Preparations according to US 4,727,088 comprise a novel vehicle system which system delivers an active ingredient to the site of action in a form whereby bioavailability and percutaneous absorption are enhanced. A retinoid compound, all-trans retinoic acid or 13-cis retinoic acid, is disclosed as the active ingredient having anti-acne activity. Thus the retinoid compound is acting as a topically active agent per se rather than contributing to the vehicle system which promotes enhanced bioavailability and percutaneous absorption.

It has now been found that retinoid compounds are themselves able to enhance bioavailability and percutaneous absorption of topically active substances and hence synergise the

effect of topically active substances.

According to the present invention there is provided a method of enhancing the bioavailability and percutaneous absorption of a topically active substance which method comprises the topical administration to the skin and/or scalp of an effective amount of a composition comprising a penetration enhancer in the form of a retinoid compound, and a topically active substance which is other than a retinoid compound.

As used herein the term topically active substance includes materials which when applied to the skin and/or scalp give rise to a cosmetic and/or therapeutic effect. Thus the term topically active substance includes materials generally regarded as conferring only cosmetic benefit and also medicaments of therapeutic value. It will of course be appreciated that certain substances, for example anti-acne treatments, may confer both cosmetic and therapeutic effects.

Compositions suitable for use in the method of the present invention include a retinoid compound and a topically active substance which substance has inter alia utility in the treatment of bacterial, fungal and viral infections; in the treatment of skin disorders such as acne, psoriasis and dermatitis; in the treatment of the effects of skin and tissue damage such as wounds and bruising; and in arresting hair-loss and promoting hair-growth.

As used herein, the term retinoid compound includes retinoic acid, in particular all trans retinoic acid and derivatives thereof including esters and amides; retinal; retinol and derivatives thereof including ethers and in particular retinol esters.

It will be appreciated that the term retinoid compound also includes, where applicable, salts, for example alkali metal salts and alkaline earth metal salts, and also solvates including hydrates.

A particularly preferred group of retinoid compounds includes retinol ester compounds. These esters, unlike retinoic acid, show very little irritancy when applied topically, and, as referred to above, have been shown to confer the additional advantage in a hair-care product of enhancing hair-growth for example by increasing the diameter of growing hair.

Preferably, a composition of the invention comprises at least one C_{2-16} alkanoyl ester of retinol.

More preferably, a composition of the invention comprises at least one C_{2-7} straight chain, branched chain or cyclic alkanoyl ester of retinol, for example retinyl acetate, propionate, butyrate, cyclopentanecarboxylate, pivalate, valerate, hexanoate or heptanoate; or retinyl palmitate.

A particularly preferred composition comprises the propanoyl or the palmitoyl ester of retinol.

The stability of retinol esters for use in topical hair-care and skin-care products may be enhanced by the selection of an appropriate carrier. Thus compositions for use in the present invention optionally include a topically acceptable carrier and in particular a topically acceptable carrier which enhances the stability of a retinol ester.

In another aspect of the invention there is provided a novel composition comprising a penetration enhancer in the form of a retinoid compound, in particular a retinyl ester or a

mixture of esters of retinol, and a topically active substance other than a retinoid compound, for topical administration.

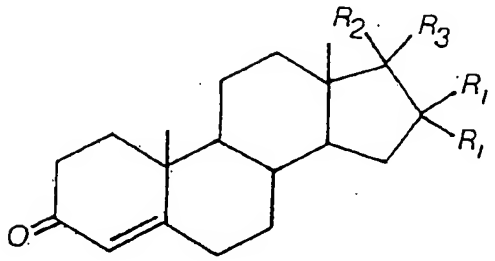
It will be appreciated that novel compositions for topical administration according to the present invention do not include specific combinations of retinoid compounds and topically active substances which form part of the state of the art, i.e. are available to the public in any way, for example via use or by being specifically described in any printed publication. Thus any specifically identified combination, for example those combinations exemplified in WO 83/02558 (Bazzano) are hereby excluded by proviso.

A novel composition according to the present invention, which is provided by way of example only and is not limited thereto, comprises a retinoid compound and a compound as described in United Kingdom Patent, GB 1 538 227 (Beecham).

United Kingdom Patent, GB 1 538 227 (BEECHAM), discloses a group of 16,16-disubstituted androstene steroid compounds having pharmaceutical activity, which particular compounds are of utility in the treatment of androgen dependent skin disorders such as acne and seborrhoea. The possible use of these compounds in the treatment of androgenic alopecia and male pattern baldness in women is proposed, but not substantiated.

It has been found that topical administration of a compound described in GB 1 538 227, in particular the compound androst-4-ene-16,16-dimethyl-17β-ol-3-one, is effective in antagonising the influences of hormones in relation to hair-growth and skin disorders and thus has the utility in arresting hair loss, in promoting hair-growth and in the treatment of acne.

GB 1 538 227 discloses compounds of formula (I):



(I)

wherein

R_1 is a C_{1-5} alkyl group, a C_{3-6} alkenyl group, a C_{3-6} cycloalkyl group, or a phenylalkyl group in which the alkyl moiety contains 1 to 3 carbon atoms and the phenyl moiety is optionally substituted; R_2 is a hydroxyl group, or a group OR_4 wherein R_4 is a C_{2-7} alkanoyl group, a C_{1-4} alkyl group, or an optionally substituted benzyl group; and R_3 is hydrogen or a C_{1-5} alkyl group; or R_2 and R_3 together with the carbon atom to which they are joined represent a carbonyl group.

Optional substituents for phenyl moieties include C_{1-4} alkyl, halogen and nitro.

Preferably R_1 is a methyl, ethyl or n- or iso-propyl group, and most preferably a methyl group.

Preferably R_2 is a hydroxyl group. Variable R_2 suitably has the β-configuration.

Preferably R_3 is hydrogen or methyl, and most preferably hydrogen.

Particularly favoured is the compound of formula (I) in which R_1 is methyl; R_2 is hydroxy and has the β-configuration; and R_3 is hydrogen, which is the compound

androst-4-ene-16,16-dimethyl-17β-ol-3-one.

Compounds of formula (I) and in particular the compound androst-4-ene-16,16-dimethyl-17β-ol-3-one are claimed to have 5α-reductase inhibitory activity but no significant androgenic, anti-androgenic or anabolic activity. The lack of systemic side-effects renders these compounds, and especially the compound androst-4-ene-16,16-dimethyl-17β-ol-3-one, particularly suitable for targeted delivery in a topically administered composition.

The above-mentioned antagonistic effects of compounds of formula (I) described in GB 1 538 227 and in particular the compound androst-4-ene-16,16-dimethyl- 17β-ol-3-one are enhanced in accordance with the present invention by the topical co-administration of a retinoid compound.

Compositions for use according to the present invention preferably include a topically acceptable carrier which is anhydrous or wherein the retinoid, more especially a retinol ester or mixture thereof, is dissolved in a non-aqueous phase of a multiphase system, which phases, on mixing, may be miscible, or may form an emulsion such as an oil-in-water or water-in-oil type of emulsion. Alternatively, the stability of a retinyl ester may be enhanced by incorporation into an aqueous gel such as a carbopol gel.

Suitably an anhydrous carrier comprises an anhydrous alcohol such as propan-2-ol or ethanol, a volatile oil such as a volatile silicone, or mixtures thereof. Suitably a non-aqueous phase of a multiphase system comprises a volatile oil such as a volatile silicone.Examples of oils suitable for inclusion in the present compositions include: volatile linear iso-paraffins, acyclic dimethylpolysiloxanes for example dimethylpolysiloxane, cyclic

dimethylpoly-siloxanes, mineral oils, vegetable oils, synthetic fatty acid esters, fatty alcohols, lanolin and its derivatives.

Where the topically active substance is insoluble or only very poorly soluble in water, it will be appreciated that where the topically acceptable carrier comprises an aqueous phase a further solvent will generally be present to solubilise the topically active substance. Suitable solvents include volatile alcohols such as ethanol and propan-2-ol and less-volatile alcohols such as benzyl alcohol.

Compositions for use according to the invention should desirably include an anti-oxidant effective in preventing oxidation of the retinoid compound and consequent reduction in the activity of the composition. Some anti-oxidants are effective in this respect but themselves oxidise to give a noticeable yellowing of the products.

Anti-oxidants which are suitable for incorporation include butylated hydroxytoluene (BHT), (2,3-di-tert-butyl-p-cresol); butylated hydroxyanisole (BHA), (2-tert-butyl-4-hydroxyanisole or 3-tert-butyl-4-hydroxyanisole); butylated hydroquinone (BHQ); tert-butylhydroquinone (TBHQ); vitamin E acetate; ascorbyl palmitate; and Nipanox (BHA: propyl gallate: citric acid:propylene glycol; 13:13:4:70)or a mixture of these. A particularly suitable anti-oxidant is Nipanox. Accordingly in another of its aspects, the invention includes a composition for use in accordance with the invention including an anti-oxidant selected from any of the above.

It may also be desirable to include a sequestering agent in compositions for use according to the invention, for example a metal ion chelator such as citric acid or ethylene diamine tetraacetic acid. When a sequestering agent and an

anti-oxidant are both present, the sequestering agent will not normally be citric acid when the anti-oxidant is Nipanox. Accordingly in another of its aspects the invention includes a composition for use in accordance with the invention including a sequestering agent.

A typical composition of the invention in which the topically active substance is a compound of formula (I), will comprise (w/w) from 0.005 to 5%, preferably 0.5 to 2.5% and more preferably 2% of a compound of formula (I) and from 0.01 to 2%, preferably 0.1 to 1.0% and more preferably 0.2% of a retinoid compound.

The compositions will optionally include (w/w) from 0.01 to 1% and preferably 0.05 to 0.25% of an anti-oxidant; and from 0.005 to 1%, and preferably 0.008 to 0.02% of a sequestering agent.

A typical single-phase formulation will additionally include an anhydrous carrier comprising (w/w) from 80 to 99.5% of an anhydrous solvent or solvent mixture.

When used herein, the terms 'liquid' and 'solution' include viscous materials such as creams, ointments and gels.

Compositions for use in the present invention may be applied topically to the skin or scalp as appropriate in the form of lotions, ointments, creams, conditioners, gels, mousses, sprays or aerosols. It will however be appreciated that topical compositions will not be limited to the forms indicated above.

A composition for topical application to the skin or scalp is preferably a 'leave-on' product, and includes, as appropriate, conditioners, tonics, lotions, creams,

dressings, gels, spray on conditioners, aerosol conditioning sprays, mousses, post foaming hair gels, styling and hairsprays.

According to the type of product required, in addition to the retinoid, the topically active substance and the optional carrier, many other topically acceptable ingredients may be used.

For example, in a skin-care product compositions may additionally contain a particulate substance such as silica, silanised silica or talc, which substance may improve the feel and appearance of a treated skin area.

Gels, conditioners and other hair dressings will contain ingredients conventionally used in the art, and may include emulsifiers, detergents and alcohol.
Additional ingredients such as perfumes and dyes may also be used.

In a particular aspect of the invention there is provided a composition comprising a retinoid compound, more especially an ester of retinol or a mixture of esters of retinol, and a compound of formula (I), in particular androst-4-ene-16,16-dimethyl-17β-ol-3-one.

Advantagously, compositions will be formulated with topically acceptable carrier materials such that the retinoid component and the formula (I) component are presented in substantially saturated or super-saturated concentrations, optionally containing an anti-nucleating agent to prevent precipitation, in order to promote penetration of the skin or scalp.

A solution substantially saturated and preferably super-saturated in one or both components may be created <u>in situ</u>

from a solution which is sub-saturated in one or both components by using a mixture of volatile and non-volatile solvents. On topical application, the volatile solvent rapidly evaporates thereby increasing the concentration of one or both components to substantially saturated and preferably super-saturated level. Suitable examples of volatile solvents include ethanol, propan-2-ol and volatile silicone fluids. Suitable examples of non-volatile solvents include propylene glycol, polyethylene glycol, silicone fluids and Arlasolve DM1 (dimethyl iso-sorbide).

Alternatively, substantially saturated and preferably super-saturated levels may be achieved by dissolving the active components in the first and/or second of two liquid phases and mixing them together either in situ post-application or immediately prior to use. The composition of the two liquid phases and the concentrations of the active components are selected such that on admixture of the two phases the concentration of one or both active components is near to or greater than the saturated solubility in the initially formed resultant mixture.

Super-saturated systems of this type are described in United States Patent No. 4,767,751, (Beecham Group plc).

It will be appreciated that where one liquid phase contains water, the stability of a retinoid compound which is a retinyl ester will be enhanced if it is dissolved in a non-aqueous second phase. Moreover, as described above, where the compound of formula (I) is dissolved in a liquid phase containing water, a further solubilising agent will be present in that phase.

Suitable anti-nucleating agents include polyvinylpyrrolidone (PVP), carboxymethyl cellulose (CMC), and hydroxypropyl methyl cellulose (HPMC).

The compositions of this invention should desirably include an anti-oxidant effective in preventing oxidation of the retinoid compound and consequent reduction in the activity of the composition. Some anti-oxidants are effective in this respect but themselves oxidise to give a noticeable yellowing of the products.

Anti-oxidants which are suitable for incorporation include butylated hydroxytoluene (BHT), (2,3-di-tert-butyl-p-cresol); butylated hydroxyanisole (BHA), (2-tert-butyl-4-hydroxyanisole or 3-tert-butyl-4-hydroxyanisole); butylated hydroquinone (BHQ); tert-butylhydroquinone (TBHQ); vitamin E acetate; ascorbyl palmitate; and Nipanox (BHA: propyl gallate: citric acid: propylene glycol; 13:13:4:70) or a misture of these. A particularly suitable anti-oxidant is Nipanox. Accordingly in another of its aspects, the invention includes a composition in accordance with the invention including an anti-oxidant selected from any of the above.

The present invention also provides a composition comprising a retinoid compound, in particular a retinyl ester, and a compound of formula (I), in particular the compound androst-4-ene-16,16-dimethyl-17β-ol-3-one, for cosmetic and/or therapeutic use.

The present invention further provides a composition comprising a retinoid compound, in particular a retinyl ester, and a compound of formula (I), in particular androst-4-ene-16,16-dimethyl-17β-ol-3-one for use as an antagonist of the influences of hormones in relation to

hair-growth and skin-disorders.

The present invention also provides a composition comprising a retinoid compound, in particular a retinyl ester, and a compound of formula (I), in particular the compound androst-4-ene-16,16-dimethyl-17β-ol-3-one for use as a skin-care product and in particular for the treatment of acne.

In addition, the present invention provides a composition comprising a retinoid compound, in particular a retinyl ester, and a compound of formula (I), in particular the compound androst-4-ene-16,16- dimethyl-17β-ol-3-one for use as a hair-care product and in particular for arresting hair-loss and/or promoting hair-growth.

The present invention provides a method of enhancing the bioavailability and percutaneous absorption of a topically active cosmetic substance which method comprises the topical administration to the skin and/or scalp of an effective amount of a composition comprising a penetration enhancer, more especially a retinyl ester or a mixture of esters of retinol, and a topically active cosmetic substance which is other than a retinoid compound.

Furthermore, the present invention provides a method of enhancing the bioavailability and percutaneous absorption of a topically active therapeutic substance which method comprises the topical administration to the skin and/or scalp of an effective amount of a composition comprising a penetration enhancer, more especially a retinyl ester or a mixture of esters of retinol, and a topically active therapeutic substance which is other than a retinoid compound.

In another aspect of the invention there is provided a method of treatment of conditions of the human and animal body which are responsive to topically active substances, which method comprises the topical administration of an effective amount of a composition comprising a retinoid compound, in particular a retinyl ester, and a topically active cosmetic and/or therapeutic substance which is other than a retinoid compound.

In a particular aspect there is provided a method of treating bacterial, fungal or viral infections in mammals including humans, which method comprises the topical administration of an effective amount of a composition comprising a retinoid compound, in particular a retinyl ester, and a topically active anti-bacterial, anti-fungal or anti-viral substance.

In addition there is provided a method of treatment of skin disorders, in particular acne, psoriasis and dermatitis, which method comprises the topical administration of an effective amount of a composition comprising a retinoid compound, in particular a retinyl ester, and a topically active anti-acne, anti-psoriasis or anti-dermatitic substance which is other than a retinoid compound.

There is also provided a method of treatment of the effects of skin and tissue damage, in particular wounds and bruising, which method comprises the topical administration of an effective amount of a composition comprising a retinoid compound, in particular a retinyl ester, and a topically active substance effective in the healing of skin and tissue damage which is other than a retinoid compound.

There is also provided a method of arresting hair-loss and/or promoting hair-growth which method comprises the topical administration of an effective amount of a

composition comprising a retinoid compound, in particular a retinyl ester, and a topically active substance effective in arresting hair-loss and/or promoting hair-growth which is other than a retinoid compound.

In a particular aspect, the present invention provides a method of treating skin-disorders, in particular acne, which method comprises the topical administration to the skin or scalp of an effective amount of a composition comprising a retinoid compound, in particular a retinyl ester, and a compound of formula (I), in particular the compound androst-4-ene-16,16-dimethyl-17β-ol-3-one.

In yet a further particular aspect, the present invention providesa method for arresting hair-loss and/or promoting hair-growth which method comprises the topical administration to the scalp of an effective amount of a composition comprising a retinoid compound, in particular a retinyl ester, and a compound of formula (I), in particular the compound androst-4-ene-16,16-dimethyl-17β-ol-3-one.

The following examples illustrate specific formulationsfor compositions for use in accordance with the present invention. In each formulation, the compound androst-4-ene-16,16-dimethyl-17β-ol-3-one is included by way of example only as a representative example of a topically active substance and is identified as 'Compound A'.

Example 1
Formulations containing retinyl propionate and Compound A

Component	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
Retinyl propionate	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Compound A	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Propan-2-ol	90.60	80.60	95.10	40.70	-	-	-	-
Silicone oil*	-	-	-	50.00	-	-	-	50.00
Benzyl alcohol	5.00	7.00	2.00	5.00	5.00	7.00	2.00	5.00
Nipanox	0.20	0.20	0.20	0.10	0.20	0.20	0.20	0.10
Propylene glycol	2.00	10.00	-	2.00	2.00	10.00	-	2.0
PVP	-	-	0.50	-	-	-	0.5	-
ethanol	-	-	-	-	90.60	80.60	95.10	40.70

Example 2
Formulations containing retinyl palmitate and Compound A

Component	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
Retinyl palmitate	0.20	1.00	0.20	0.20	0.20	1.00	0.20	0.20
Compound A	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Propan-2-ol	40.70	46.90	95.10	40.69	-	-	-	-
Silicone oil*	50.00	50.00	-	50.00	50.00	50.00	-	50.00
Benzyl alcohol	5.00	5.00	2.00	5.00	5.00	50.00	2.00	5.00
Nipanox	0.10	0.10	0.20	0.10	0.10	0.10	0.20	0.10
Sequestering agent	-	-	-	0.01**	-	-	-	0.01**
Propylene glycol	2.00	2.00	-	2.00	2.00	2.00	-	2.00
PVP	-	-	0.5	-	-	-	0.5	-
ethanol	-	-	-	-	40.70	46.90	95.10	40.69

*Polydimethylsiloxane (200/0.65)
** Ethylene diamine tetraacetic acid

Claims

1. A method of enhancing the bioavailability and percutaneous absorbtion of a topically active substance which method comprises the topical administration to the skin and/or scalp of an effective amount of a composition comprising a penetration enhancer in the form of a retinoid and a topically active substance which is other than a retinoid.

2. Use of a retinoid as a penetration enhancer in the manufacture of a medicament for enhancing the bioavailability and percutaneous absorption of a topically active substance, said topically active substance is other than a retinoid.

3. Use as claimed in claim 2, wherein said topically active substance has utility in the treatment of bacterial, fungal or viral infections, or in the treatments of skin disorders such as acne, psoriasis and dermatitis, or in the treatment of the effects of skin and tissue damage such as wounds and bruising; or in arresting hair loss or promoting hair growth.

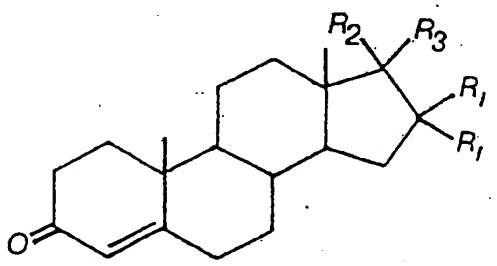
4. Use as claimed in claim 2 or 3 wherein the retinoid is selected from the group, retinoic acid and derivatives thereof including esters and amides retinal; retinol and derivatives thereof including ethers and retinol esters.

5. Use as claimed in claims 2 to 4 wherein the retinoid is an C_{2-16} alkanoyl ester.

6. Use as claimed in claim 2 to 5 wherein the retinoid is the propanoyl or the palmitoyl ester of retinol.

7. A pharmaceutical composition comprising a penetration enhancer in the form of a retinoid, and a topically active substance other than a retinoid and a pharmaceutical carrier with the proviso that the topically active substance is not minoxidil.

8. A pharmaceutical composition comprising retinoid and a topically active substance selected from a compound of formula (I):



(I)

wherein

R_1 is a C_{1-5} alkyl group, a C_{3-6} alkenyl group, a C_{3-6} cycloalkyl group, or a phenylalkyl group in which the alkyl moiety contains 1 to 3 carbon atoms and the phenyl moiety is optionally substituted; R_2 is a hydroxyl group, or a group OR_4 wherein R_4 is a C_{2-7} alkanoyl group, a C_{1-4} alkyl group, or an optionally substituted benzyl group; and R_3 is hydrogen or a C_{1-5} alkyl group; or R_2 and R_3 together with the carbon atom to which they are joined represent a carbonyl group.

9. A pharmaceutical composition as claimed in claim 8 wherein R_1 is methyl ethyl, or n- or iso propyl; R_2 is hydroxy and has the β-configuration; and R_3 is hydrogen or methyl.

10. A pharmaceutical composition as claimed in claim 8 or 9 wherein the compound is androst-4-ene-16,16 dimethyl-17β-ol-3-one.

11. A pharmaceutical composition as claimed herein wherein the carrier is an anhydrous carrier.

12. A pharmaceutical composition as claimed herein wherein the retinoid is dissolved in a non-aqueous phase of a multiphase system.

13. A composition as claimed in any of claims 8 to 10 for use as an antagonist of the influences of hormones in relation to hair growth and skin-disorders.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01874

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 47/06, 31/07, 31/56

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP, A2, 0391033 (J. YU RUEY ET AL) 10 October 1990, see the whole document --	1-13
A	EP, A2, 0339905 (ETHICON INC.) 2 November 1989, see the whole document --	1-13
A	GB, A, 1538227 (BEECHAM GROUP LIMITED) 17 January 1979, see the whole document --	1-13

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* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24th February 1992	06. 03. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Danielle van der Haas

ANNEX TO THE INTERNATIONAL SEARCH REPORT, ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 91/01874

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/12/91 The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

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EP-A2- 0391033	10/10/90	AU-D-	4914690	11/10/90
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		AT-B-	368524	25/10/82
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